The riddle of schizophrenia

This is not a treatise on how to diagnose schizophrenia nor on how to manage it. The assemblage of symptoms and behaviours which is likely to attract the diagnosis of schizophrenia, and the possible reasons for its existence, raise many questions. Here are some of those questions and the progress made in answering them.

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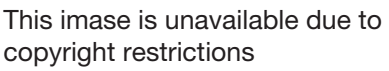
Schizophrenia cannot be ignored. It affects about one in a hundred of the world's population. The 1990 WHO survey of the global burden of disease ranks schizophrenia ninth in the causes of disability.[1] It kills people: one study showed that 5% of people with chronic schizophrenia suicide compared with 0.8% of the general population.[2]

The financial costs are difficult to estimate. Definitions of schizophrenia change from time to time and, as we shall see, the condition itself changes. There is no doubt that some sufferers escape a formal diagnosis, being regarded as no more than eccentric or difficult. Medication has cut the costs by improving the outcome. Another way of saving money is to close some treatment facilities and not fund alternatives. Some governments find this attractive.

There are the direct costs of hospitalisation and medication, as well as the costs of lost productivity, for many people with schizophrenia are unem-

IN SUMMARY

- **The problem with definitions of schizophrenia is that many individuals have one foot inside and one foot outside the boundaries. The individuals – like the definitions themselves – change with time.**
- **The range of symptoms is very wide. Some have florid hallucinations and delusions, others are blunted and emotionally flat. Depression is common, but some patients are elated.**
- **MRI and PET studies have suggested disturbed neural circuitry in the prefrontal regions, the thalamic nuclei and the cerebellum.**
- **It is clear that there is a genetic vulnerability to schizophrenia, but no-one knows its precise weighting.**
- **Other putative causes of schizophrenia are low levels of vitamin D in utero, and maternal infection with influenza in the second trimester. Speculations abound.**



These painted stones are testimony to the suffering of a schizophrenic woman who used to pick up stones as she scurried along, fleeing from contact with other people. She gathered them in their dozens and formed their notches and bulges into demonic faces. She was beset by these grimacing stone faces everwhere in her home. Not a nook was free of them. The patient was imprisoned in a delusional world she had created for herself out of stone 'faces'.

F. GNIRSS. PAINTINGS ON STONES BY A PATIENT WITH PARANOID PSYCHOSIS. IN: PSYCHOPATHOLOGY AND PICTORIAL EXPRESSION, AN INTERNATIONAL ICONOGRAPHICAL COLLECTION. © NOVARTIS AG, BASEL: SWITZERLAND.

ployed. In 1987, an estimate of the direct and indirect costs of schizophrenia in the UK was £1296 million per year.[3] There are also the costs of personal suffering and family disorganisation. There is no doubt that schizophrenia is a very expensive disorder.

How does one define schizophrenia?

Precise definitions of schizophrenia can be found in a number of compendiums of psychiatric nosology. The problem is that the definitions are not in complete agreement and they change with each edition. More importantly, there are many individuals who seems to have one foot inside and one foot outside the boundaries: they too change with time.

To take one facet of the problem, early definitions of schizophrenia – a century ago and more – described it as a dementing disease. It was called 'dementia praecox' and it was thought by some that the dementia was due to grossly excessive masturbation which damaged the nervous system irretrievably. Less enthusiastic masturbation merely exhausted the nerves and one developed neurasthenia.[4]

But is there a cognitive loss? Recent studies report on a group of children whose intelligence was tested at the age of 4 years and who were then followed into young adulthood. Those who showed a definite decline in IQ during childhood showed an increased likelihood of developing psychotic symptoms. To put it shortly, there is often a cognitive loss which can be demonstrated at the beginning of the manifest illness and which does not advance.[5] Nevertheless, a few patients seem to dement.

The most recent review of postmortem findings produced some important observations. Schizophrenia itself is not characterised by a classical histologically identifiable neuropathology. When there is dementia in schizophrenia, in most cases it is not the result of a neuropathologically identifiable process.[6]

The bottom line is: it is clear what the dementia of schizophrenia is not, but what it is remains quite unclear. There is a mystery.

The wide range of symptoms

Achieving an acceptable definition of schizophrenia bedevils every study. The variation from patient to patient is very wide. Some respond rapidly and well to medication, some pursue a relentless downhill course. Some have florid hallucinations and delusions, others are blunted and emotionally flat. Some make their way in the world quite successfully, others are invalids. Most are in the middle.

Depression is common, as one might imagine, but some patients are elated. Whereas there was once thought to be a clear boundary between 'schizophrenia' and 'manic depressive psychosis', to use the older term, now there is not. The diagnosis of 'schizoaffective disorder' encapsulates this overlap. It would have been unthinkable to Bleuler and Kraepelin.

Again there are those who exhibit some of the phenomena of schizophrenia without qualifying for a formal diagnosis. The current term for this group is schizotypal personality disorder. Surely they evidence the fuzzy boundaries of the definition – we are dealing with dimensions rather than a category.

What is the pathology?

The first effective antipsychotic drugs – the phenothiazines – arrived in the middle of this century. Since they affected the metabolism of the neurotransmitter dopamine, it was argued that either too much dopamine was being released at the relevant synapses or that the postsynaptic dopamine receptors were hypersensitive.

Enthusiasm led to the view that schizophrenia was a neurotransmitter disturbance in a normal brain – it was a 'chemical imbalance'. Neuroimaging has overturned that simple hypothesis: we know now that there are anatomical changes and that we must think of disturbed neural circuitry rather than simple chemical errors.

Recent studies involving both MRI and positron emission tomography have suggested that there is disturbed neural circuitry involving prefrontal regions, the thalamic nuclei and the cerebellum. It is important to understand that there is good evidence to suggest that the cerebellum is involved in quite complex cognitive activities such as facial recognition and cognitive planning.[7]

The indefinite boundaries of the clinical syndrome are reflected in the neuroimaging studies. People with schizophrenia have larger lateral ventricles than most of their relatives and normal controls. But some clinically well relatives show the same enlargement, particularly if there is reason to believe that they may be carriers of the disorder. For example, the well mother of a patient who herself has a parent with schizophrenia may have enlarged ventricles, but no evidence of the schizophrenic process.[8] She may be at risk, but the disorder has never arrived.

Put simply, it seems that in schizophrenia there is a brain lesion present before the manifest illness. Something has gone wrong during brain development. Further evidence suggests that the abnormality is not progressive. The enlargement of the cerebral ventricles and the other changes demonstrable at the onset of the illness are fixed and there is no evidence of an active pathological process in most postmortem studies. What is going on?

Is schizophrenia a new disorder?

In looking for a cause of these changes it would be instructive to know if the clinical picture we see now has been unchanged over the centuries or if we are encountering something relatively

new, like HIV. Is it a recent plague?

Certainly its presentation has changed greatly in the last half century. I began to see patients with acute schizophrenia in 1944. They were servicemen and servicewomen, almost all of whom had been performing well enough until days or weeks before they came to notice. We were seeing schizophrenia at presentation.

They were very disturbed indeed. Their thinking and their conversation were fragmented; their behaviour was grossly disordered and some were dangerous. Extrapyramidal syndromes were usual and obvious catatonia was quite frequent. Interestingly, all the extrapyramidal phenomena we see now as a consequence of psychotropic medication we saw then as an integral part of schizophrenia. The neuroleptic malignant syndrome we encounter now was then described as the secondary lethal catatonia of Stauder – patients died from it.

There have been more subtle changes. In those days patients with auditory hallucinations spent some of their time searching for the source of the voices. You would see them standing on chairs looking into ventilators or poking under buildings with sticks. Few do that nowadays; almost always patients locate the voices inside their heads.

What about the more distant past?

Looking further backwards is more difficult than you might imagine. Behaviour must be judged against the standards of the day. For example, in the 17th century two Presidents of the Royal College of Physicians were astrologers who cast their patients' horoscopes as part of the consultation.[9] The general practitioner, whose clinical notes give us most insight into the disorders of the day, not only cast horoscopes but also consulted frequently with the Archangel Raphael.[10] If one were to do this nowadays it would not be surprising if one's colleagues were to ring the Doctors' Health Advisory Service.

Again, words change their meanings as the years pass. It was one thing to be gay a century ago, but it is something else now. Understanding the clinical notes of another age keeps one close to the seventeen volumes of the Oxford English Dictionary in which the changes in meaning with time are to be found.

Again, the delusions and hallucinations recorded in those days may well have been the product of coarse brain disease, diagnosable with modern investigations. The best that could be done then was to divide madness into two categories – cases with fever and cases without.

It is noteworthy, I believe, that the first edition of Haslam's *Observations on madness and insanity* does not have a description of a schizophrenic patient but certainly the second one in 1809 contains a desc-ription of 'a form of insanity of young people that transforms the most promising and vigorous intellect into a slavering and bloated ideot'.[11] Moreover at about the same time the numbers in the various institutions of the day began to rise very rapidly. Opinions differ, but I share the view of those who believe that an epidemic of psychosis began then, became rampant and continued until the middle of this century, when it began to moderate not in frequency but in severity.

What can have produced the epidemic? It seems clear that there is a genetic vulnerability to schizophrenia. Everyone agrees that it exists but no-one knows its precise weighting. Once again, the indefinite boundaries of the disorder stand in the way of a precise answer. Quite certainly there is no single gene – there are monozygotic twins discordant for schizophrenia. Epigenetic causes have been suggested recently; their complexities are beyond the scope of this article.[12]

We might ask ourselves about other possible causes of an error in neurodevelopment. There is some evidence to suggest that birth injury can play a part. At least in some countries maternal influenza in the second trimester has been found to be associated both with the changes in the brain morphology associated with schizophrenia and with the later development of the illness.[13] Interestingly, there is also evidence to suggest that maternal influenza is associated with the later development of affective disorder.[14]

Recently, it has been suggested that low levels of vitamin D *in utero* also may be associated with the later development of schizophrenia.[15] One wonders if there are not many more influences on fetal development which may have all the same consequences.

Another possibility is that there is some sort of slow infection – a virus, a prion, perhaps. This is consistent with a seasonal variation in the time of birth of people who develop schizophrenia observed in some countries. It offers a reason for changes in the severity of the disorder over the past few centuries – perhaps an infective agent appeared and is now disappearing, or we are gaining some immunity to its attack.[16] Speculations abound.

It has long been known that people with schizophrenia have more neurological soft signs and show greater deficits on a variety of neuropsychological tests than normal controls and mixed groups of psychiatric patients. In a recent study, those with the larger deficits were the patients who responded poorly to conventional antipsychotics. Once again, there is persuasive evidence of something being wrong with the brain, but no clue as to how many noxious influences there may be.[17]

Conclusion

The word schizophrenia encompasses a universe of suffering and unresolved questions. I think of it not as a diagnosis but as a useful term, pointing us in the direction where something practical may be done. It is a term like anaemia, epilepsy and arthritis – it heralds the beginning of a search. One can achieve the appearance of a precise category of schizophrenia by disregarding much of the data. This may be good enough for research but not for the individuals who come to us for understanding and help. They are people with all the complexities of the human condition, disturbed and confounded by a developmental error in their brain. MT

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